

**The NCI Office of Cancer Complementary and
Alternative Medicine**

Invited Speaker Series

**Acupuncture Research:
Examples of the State of the Science
from Bench to Bedside**

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INTRODUCTION

The National Cancer Institute's Office of Cancer Complementary and Alternative Medicine (OCCAM) hosted *Acupuncture Research: Examples of the State of the Science from Bench to Bedside*, the first session in its Invited Speakers Series on complementary and alternative medicine research. On January 17, 2002, in Lipsett Auditorium at the National Institutes of Health (NIH), a panel of international experts in acupuncture research presented data from animal studies and some of the latest in clinical practice.

An Overview of the Acupuncture Literature

*Brian Berman M.D., Professor, Family Medicine, and Director,
Complementary Medicine Program, University of Maryland*

Summary

Acupuncture is a 3,000-year-old component of Chinese medicine. *New York Times* reporter James Reston raised the American public's awareness of acupuncture in 1971 when he wrote about his emergency appendectomy in China and how three acupuncture needles relieved his postoperative pain.

Research during the 1970s and 1980s linked acupuncture with the central nervous system release of endogenous opioid peptides and biogenic amines, reducing some of the skepticism about acupuncture among those in the scientific community. By 1994 acupuncture was no longer classified as an experimental procedure, and in 1997 an NIH Consensus Conference named areas of high-priority research for acupuncture, including acute pain, postoperative pain, and prevention of chemotherapy-related nausea and vomiting. Today NIH, through the National Center for Complementary and Alternative Medicine, funds 11 acupuncture clinical trials.

The University of Maryland's Complementary Medicine Program conducts acupuncture research that includes randomized controlled trials of the effects of acupuncture on osteoarthritis of the knee and on pain control after oral surgery; studies of acupuncture and electroacupuncture mechanisms; and systematic reviews of acupuncture research in the literature to evaluate its scientific soundness.

Acupuncture Clinical Trials: Challenges and Strategies

*Lixing Lao, Ph.D., L.Ac., Associate Professor,
Complementary Medicine Program, University of Maryland*

Summary

Western medicine and traditional Chinese medicine are very different systems. The focus of western medicine is on disease specificity, laboratory indications, standard criteria, and standard treatment. Traditional Chinese medicine uses differentiation, a four-component diagnostic approach, and individualized conditions and treatment.

Methodological challenges in acupuncture research include inadequate sample size, lack of definitive criteria, inadequate randomization, lack of standardized outcome measures, inappropriate treatments and control groups, and insufficient follow-up time. To address these issues, the University of Maryland Complementary Medicine (CM) Program follows a modified phase-III approach determined by the Food and Drug Administration for pharmaceuticals.

Phase I clinical trials for acupuncture establish the adequate treatment dose, the range needed to determine an outcome, a sufficient follow-up period, and safety. Phase II clinical trials, which can be randomized, determine the best control group for a study, and obtain more information on safety, dosing, and preliminary efficacy. Phase III clinical trials are randomized, definitive efficacy trials that require large sample sizes.

CM acupuncture clinical trials (pilot studies through phase III) conducted over the last decade use three main models: Osteoarthritis of the knee (chronic pain, study subjects aged 50 and older), postoperative dental pain (acute pain, study subjects aged 18–40), and chemotherapy-induced nausea and vomiting (non-pain condition).

Four main components of good clinical trials for acupuncture are:

- Appropriate staging of the trial design.
- Adequate acupuncture treatment and appropriate control group for the study question.
- Good clinical trial guidelines, including adequate randomization and allocation concealment, standard blinding procedures, adequate sample size, and an appropriate follow-up period.
- Collaboration among experienced complementary and alternative medicine practitioners and investigators.

Acupuncture Analgesia: What We Have Learned from Animal Studies

*Grant Zhang, Ph.D., L.Ac., Assistant Professor, Complementary
Medicine Program, University of Maryland*

Summary

For 25 years the study of acupuncture analgesia has benefited from animal studies for the following reasons:

- Animals offer reliable pain-assessment. Tail-flick response in rat and mouse, head-jerk in rabbit, hot-plate test and vocalization in mouse, and paw withdrawal latency in rat. In these tests, noxious stimuli are applied to tail, nose, and paw, and the time between application and animal response is a measure of pain threshold.
- Animals demonstrate various pain models. In the rat these include persistent inflammatory hyperalgesia, inflammatory arthritis, persistent neurological pain, and cancer pain.
- Modern technology is available to indicate study progress, including target-specific lesions, nerve cell activity recording, genetic techniques, cellular marker tracing, and functional MRI.
- Control groups are feasible. Control group design is a major methodological weakness of acupuncture clinical trials. Control groups used in animal studies include sham control, point-specific control, procedure control (similar to sham control but without needle insertion), vehicle control (drugs or reagents), naive control (normal animal with no treatment).

From animal studies, researchers have learned that acupuncture analgesia is caused by opioid release and that the acupuncture effect is conducted through type II and III afferent (sensory) nerves. Current proposed mechanisms of acupuncture-induced analgesia include neurotransmitter release (for example, opioids), gate control

at the spinal cord, and modulating activities of functional central nervous system structures (for example, the brain's arcuate nucleus).

Limitations of animal studies include the use of normal animals with no pathological conditions, transient (minutes) pain, and the possibility that restraining the animals may produce stress-induced analgesia, which involves opioid release. To overcome these limitations the complementary medicine program uses two pathological animal models.

The localized inflammatory hyperalgesia model provides a pathological condition, acute and subacute conditions (up to 10 days), and non-restrained animals; hyperalgesia can be assessed quantitatively. The inflammatory arthritis model (systemic inflammation) is pathologically similar to human rheumatoid arthritis. There is a 5–7 day incubation period, the disease runs a 4–6 week chronic course, and immunological assays are available.

More animal studies are needed to elucidate the acupuncture mechanism.

Future Directions in Acupuncture Research: Applicability to Cancer-Related Treatment

*Richard Hammerschlag, Ph.D.,
Research Director, Oregon College of Oriental Medicine*

Summary

Over the next decade, clinical research in acupuncture will improve in the following five areas:

1. Quality of clinical trial design. The National Center for Complementary and Alternative Medicine (NCCAM) has funded seven proposals (for carpal tunnel syndrome, fibromyalgia, low back pain, and other topics) based on its 1998 RFA to improve methodology in acupuncture clinical trials. Improvements are also arising from systematic reviews of acupuncture research, and complementary and alternative medicine practitioner training in research design and research methodology at NCCAM centers.

2. Clinical research will reflect clinical practice. Acupuncture is beginning to be tested in a way that mirrors how treatment is actually delivered in clinical practice. Chinese medicine is a major proponent of individualized care, and studies are starting to include this in clinical trial design by comparing placebo, standardized treatment, and individual treatment.

3. Clinical trial reporting of acupuncture studies in scientific journals. Standards for Reporting Interventions in Controlled Trials of Acupuncture (STRICTA)—developed in the United Kingdom and to be published in biomedical journals—are guidelines, fine-tuned for acupuncture, about what must be included in clinical trials.

4. Testing acupuncture and herbs as adjunctive care for cancer-related symptoms and side effects of biomedical treatment. In this area, five areas of research need improvement:

- Examine traditional Chinese medical treatment of the body, not the disease.

- Reduce cancer symptoms (pain, cancer-related breathlessness, depression).
- Potentiate biomedical treatment.
- Use acupuncture before and after chemotherapy to suppress side effects (nausea, fatigue, neutropenia, dry mouth).
- Examine the prevention potential of green tea extracts, Chinese herbs, and other nontraditional substances.

5. Testing traditional Chinese medicine as an adjunctive system of care. It is important to understand the physiology of acupuncture's ameliorating effects on cancer-related symptoms and to know what acupuncture can reveal about how body functions that the biomedical model has not yet discovered.

Acupuncture challenges the biomedical model. It is energy-based rather than cellular-based medicine. Clinical effectiveness can occur without biomechanical transduction. Acupuncture promotes healing in a homeostatic manner. Acupuncture seems to stimulate a self-regulatory system that may be a composite of responses by the sympathetic, parasympathetic, immune and endocrine systems, or it may be an independent system.

Speaker Presentations

An Overview of the Acupuncture Literature

Brian Berman, M.D.

Director

Complementary Medicine Program

University of Maryland Medical School

NCI

January 17, 2002

Acupuncture Background

- Historical Use
- U.S. FDA decision on acupuncture needle upgrade
- NIH Consensus Conference
- Growing Worldwide Use
- NIH NCCAM currently funding 11 clinical trials involving acupuncture

U.M.B. Acupuncture Research

1) Randomized Controlled Trials

- Acupuncture and osteoarthritis of the knee. (Berman)
- Cost-effectiveness of and long-term outcomes following acupuncture treatment for osteoarthritis. (Hochberg)
- Evaluation of acupuncture for pain control after oral surgery. (Lao)
- Effect of electroacupuncture as an adjuvant for treating cyclophosphamide-induced emesis in ferrets. (Lao)

U.M.B. Acupuncture Research (cont'd)

2) Mechanisms

- Electroacupuncture attenuates behavioral hyperalgesia and selectively reduces spinal Fos protein expression in rats with persistent inflammation. (Lao)
- Local opioid receptor antagonists block acupuncture analgesia. (Zhang)
- Cerebral activity associated with acupuncture analgesia for experimental pain. (Morganstein)

U.M.B. Acupuncture Research

(cont'd)

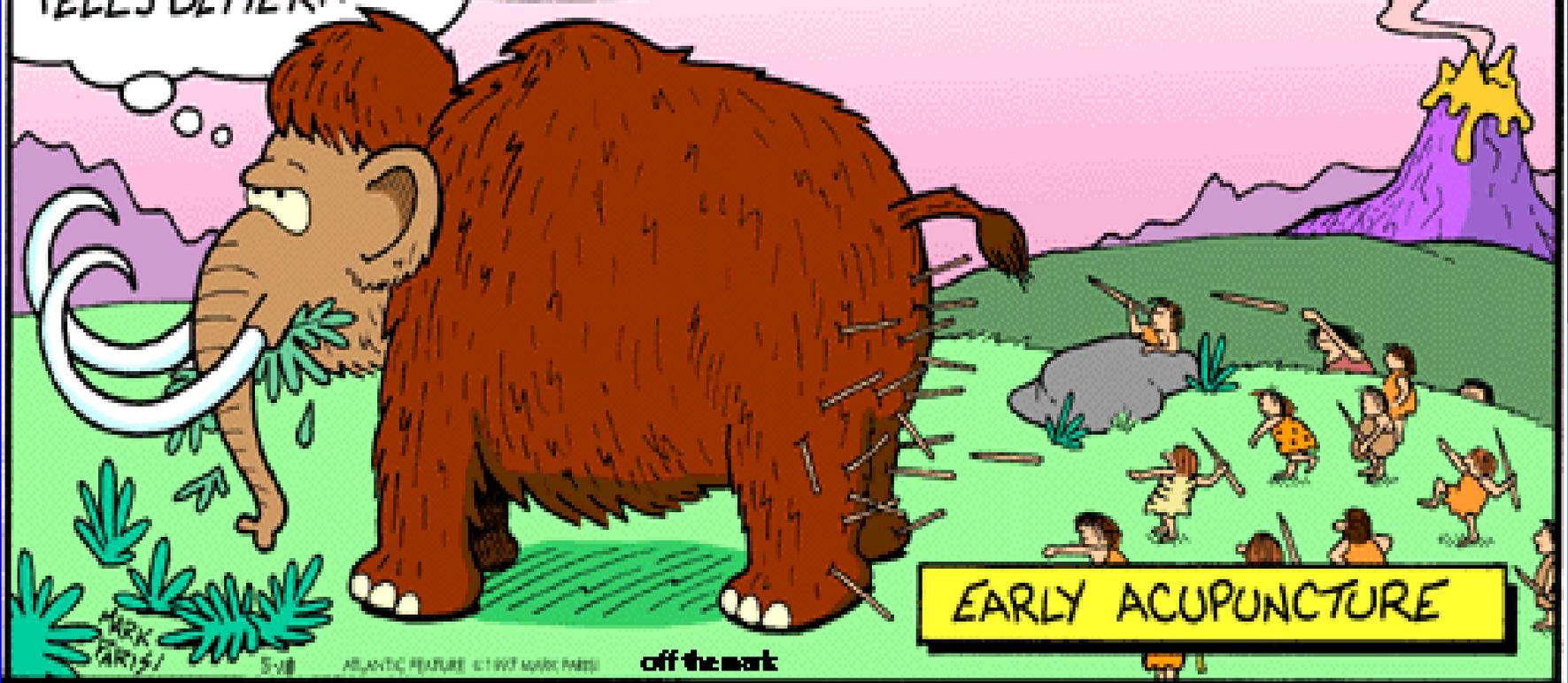
3) Systematic Reviews

- Is acupuncture effective in the treatment of fibromyalgia? (Berman)
- Is acupuncture effective for the treatment of chronic pain? A systematic review. (Ezzo)
- The effectiveness of acupuncture in the management of acute and chronic low back pain. A systematic review within the framework of the Cochrane Collaboration Back Review Group. (van Tulder)
- Acupuncture for recurrent headaches: a systematic review of randomized controlled trials. (Melchart)
- Acupuncture for osteoarthritis of the knee: a systematic review. (Ezzo)
- Systematic reviews of complementary therapies – an annotated bibliography. Part I: Acupuncture. (Linde)
- Systematic review of acupuncture for antiemesis. (Lao)

What is a Systematic Review?

A systematic review takes all the available evidence, categorizes it by how scientifically sound it is, and then makes summary statements

THAT'S ODD... MY NECK SUDDENLY FEELS BETTER...



EARLY ACUPUNCTURE

MARK PARISI

5-28

ATLANTIC FEATURE ©1997 MARK PARISI

off the mark

A Summary of the Results of Systematic Reviews of Acupuncture

- 1) Acupuncture for Painful Conditions
- 2) Acupuncture for Other Conditions

Systematic Reviews of Acupuncture and Pain Disorders

Disorder	Author	# Trials	Results
Chronic Pain	Patel, 1989	14	Inconclusive
	Ter Reit, 1990	51	Inconclusive
	Ezzo, 2000	51	Inconclusive
Low Back Pain	Ernst, 1998	12	Positive
	Tulder, 1999	12	Inconclusive
Osteoarthritis	Ernst, 1998	13	Inconclusive
	Ezzo, 2000	14	Positive/Inconclusive
Fibromyalgia	Berman, 1999	7	Positive
Dental Pain	Ernst, 1998	16	Positive
Headache	Melchart, 1999	22	Positive trend

Systematic Reviews of Acupuncture and Other Disorders

Disorder	Author	# Trials	Results
Asthma	Kleijen, 1991	14	Inconclusive
	Linde, 1996	14	Inconclusive
Nausea and Vomiting	Vickers, 1996	33	Positive
Tobacco Addiction	White, 1997	16	Negative

Why So Many Inconclusive Results?

Methodological Problems

- Inadequate acupuncture treatment
- Inappropriate control groups
- Sample size too small for adequate statistical power
- Inadequate randomization
- Allocation of groups not concealed
- Outcomes assessor not blinded
- Inappropriate follow-up time
- Attrition rates not factored into results

Features and Types of Clinical Trials According to Food Drug Administration (FDA) Nomenclature

Type	Key Features
Phase I	Preliminary information on chemical action, appropriate dose, and safety, typically not randomized, first human studies, usually do not have a control group.
Phase II	Preliminary efficacy information, more information on dose and safety, may randomize. Larger than Phase I, but still generally small.
Phase III	Assess dose effects, evaluate long term safety and efficacy, randomized. Treatment must demonstrate favorable risk/benefit ratio.

Acupuncture Clinical Trials: Challenges and Strategies

NCI CAM Research Conference

January 17, 2002



Lixing Lao, Ph.D., L.Ac.

Associate Professor

Complementary Medicine Program

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West meets the East – Western ruler and Eastern distances

Western Medicine	Traditional Chinese Medicine
<i>Disease Specificity</i>	<i>Differentiation (Syndrome)</i>
<i>Laboratory indications</i>	<i>Four diagnostic approach</i>
<i>Standard criteria</i>	<i>Individualized condition</i>
<i>Standard treatment</i>	<i>Individualized treatment</i>

Methodological Issues

- Inadequate sample size
- Lack of definitive criteria
- Inadequate randomization
- Lack of standardized outcome measures
- Inappropriate acupuncture treatments
- Inappropriate control groups
- Insufficient follow-up time

Phase I – Clinical Trials

- Adequate Dose
- Outcomes – range needed
- Follow-up period
- Safety

Phase II Clinical Trials

- Control group
- Information on safety and dosing
- Preliminary information on efficacy
- May randomize

Phase III Clinical Trials

- Definitive efficacy trials
- Randomized
- Large numbers; often multi-site

Acupuncture Trials Conducted in CM Program University of Maryland

- Osteoarthritis of the knee
 - Chronic Pain
- Post-operative dental pain
 - Acute pain
- Chemotherapy induced N/V
 - Non pain condition

Pain Models

- Knee OA – chronic pain
 - elderly population (age ≥ 50 y. o.)
- Postoperative Dental Pain – acute pain
 - younger population (age 18-40 y. o.)

Clinical Trials of Acupuncture for Osteoarthritis

Efficacy of Traditional Chinese Acupuncture in the Treatment of Symptomatic Knee OA: A Pilot Study

Berman et al, 1995 Osteoarth & Cartilage

- N = 12
- Open study
- Preliminary data on efficacy and tolerability of the treatment (8 weeks, 2x/wk acupuncture)
- Significant decrease in reports of pain & stiffness
- Significant increase in physical functioning

Establishing an Adequate Dose

- Formula vs. individual treatments
- Training/experience of acupuncturist
- Selection of points
- Total number of treatments
- De qi elicited

Choosing Follow-up Time

- Depends on condition being treated
- Depends on chronicity

Measuring Safety

- Have an explicit and systematic methodology to document side effects
- Symptoms checklist

Clinical Trials of Acupuncture for Osteoarthritis (Cont.)

A Randomized Trial of Acupuncture As an Adjunctive Therapy in OA of the Knee

Berman et al, 1995 Rheumatology

- N = 73
- Acupuncture & standard care vs. standard care alone
- Standard outcome measurements
- Confirmed findings in the pilot study
- Improvements evident at 4 & 8 wks, maintained at 12 wks
- No adverse events reported

Selecting an Appropriate Control Group

- Waiting lists (delayed treatment)
- Nonacupuncture inert controls (sham TENS, sugar pills)
- Placebo acupuncture
- Sham acupuncture
- Active controls (standard medical care)
- Combined controls

Waiting List (delayed treatment)

Question: Is acupuncture better than no treatment?

Advantages: Controls for improvements due to spontaneous remissions

Disadvantages: Cannot measure placebo effects

Clinical Trials of Acupuncture for Osteoarthritis (Cont.)

The Safety and Efficacy of Acupuncture for the Treatment of Osteoarthritis of the Knee

PI: Brian Berman, MD

- Three arm parallel design: (N = 570)
 - 1) Real acupuncture
 - 2) Sham acupuncture control
 - 3) Attention / education control group
- Multi-site
- Patients randomized by computer
- Outcomes assessor blinded to group assignment

Real Acupuncture



Real Acupuncture



Placebo/Sham Acupuncture



Placebo/Sham Acupuncture



Clinical Trials of Acupuncture for Post-operative Dental Pain

The Effect of Acupuncture on Post-operative Oral Surgery Pain: a Pilot Study

Lao et al, 1994 Acupuncture in Medicine

- N = 12
- Clear inclusive/exclusive criteria
- Preliminary data on effect of the treatment
- Test non needle insertion placebo control
- Standard patient self-reported pain
- Pain-free time: Acupuncture: mean=212min
Control: mean=65min

Clinical Trials of Acupuncture for Post-operative Dental Pain (Cont.)

The Efficacy of Chinese Acupuncture on Post-operative Oral Surgery Pain

Lao et al, 1995 Oral Surg Oral Med Oral Pathol

- N = 22
- Widely used and accepted pain model
- Randomized clinical trial
- A placebo acupuncture control
- Standard patient self-reported pain
- Significant longer pain-free time in acupuncture as compared to the control (181min vs 71min)

Placebo Acupuncture (non needle insertion)

Question: Is acupuncture more effective than placebo?

Advantages:

- Resembles real acupuncture
- Patients can be blinded
- Eliminates possible non specific needling effects

Disadvantages: Difficult to implement in long term studies
Can't be a control group for assessing acupuncture specificity

Clinical Trials of Acupuncture for Post-operative Dental Pain (Cont.)

Evaluation of acupuncture for pain control after oral surgery: a placebo-controlled trial (N=42)

Lao et al, 1999 Arch Otolaryngol Head Surg

- Randomized
- Definitive Criteria
- Sufficient Sample Size
- Patient Blind
- Dentist Blind
- Placebo Validated
- Sufficient Follow-up
- Standardized Assessment
- Dual Sited

Standardized Outcome Assessment

- Cooper- Beaver 4 Point Pain Scale
- Survival Time
- Pain Medication Recorded

Acupuncture Procedure

- Ipsilateral Points
 - Hegu (LI 4)
 - Jiache (St 6)
 - Xinaguan (St 7)
 - Yifeng (SJ 17)
- Mock ES

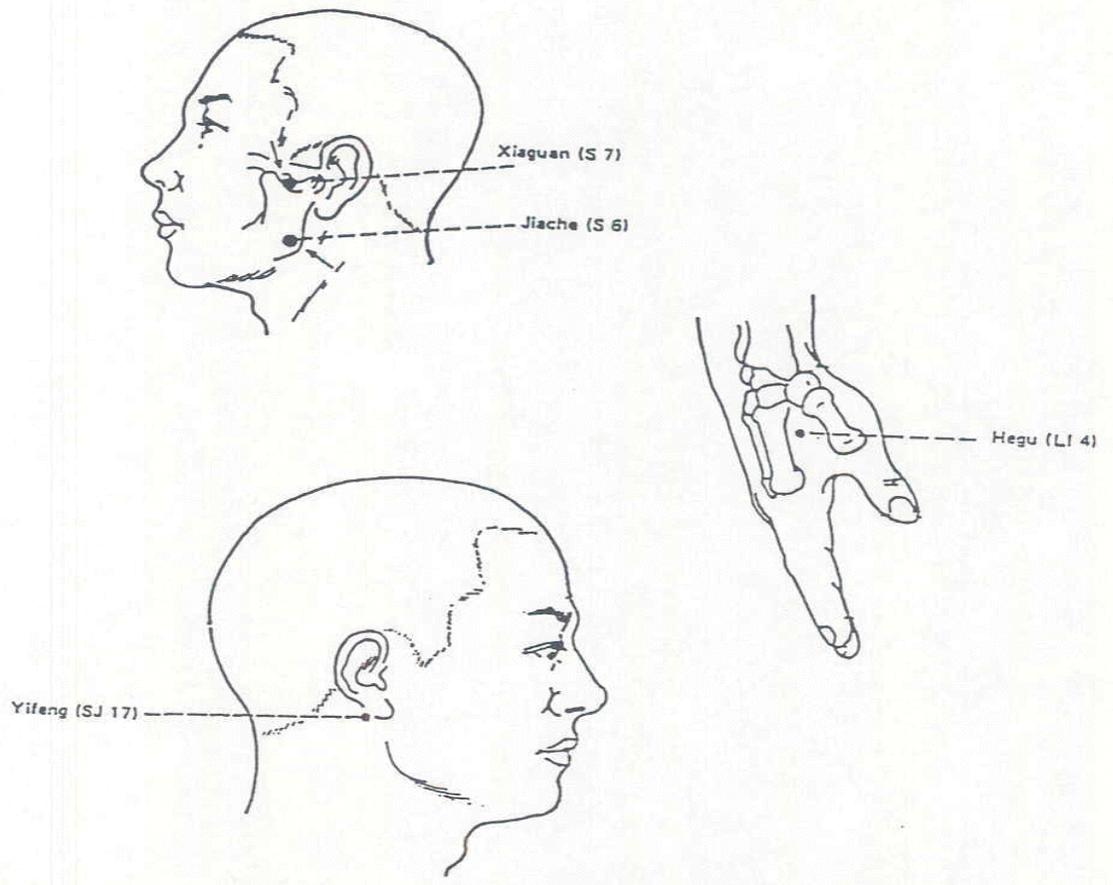


Fig. 1. Acupuncture points. Diagrams are modified from Chinese Acupuncture and Moxibustion by Cheng X. ed., 1st ed., Foreign Languages Press: Beijing, 1987.

Placebo Procedure

- Similar to Acupuncture Treatment
- No Needle Insertion

Placebo Acupuncture



Placebo Acupuncture



Placebo Validation

- Acupuncture
- Placebo
- Uncertain
- Reason for Choice

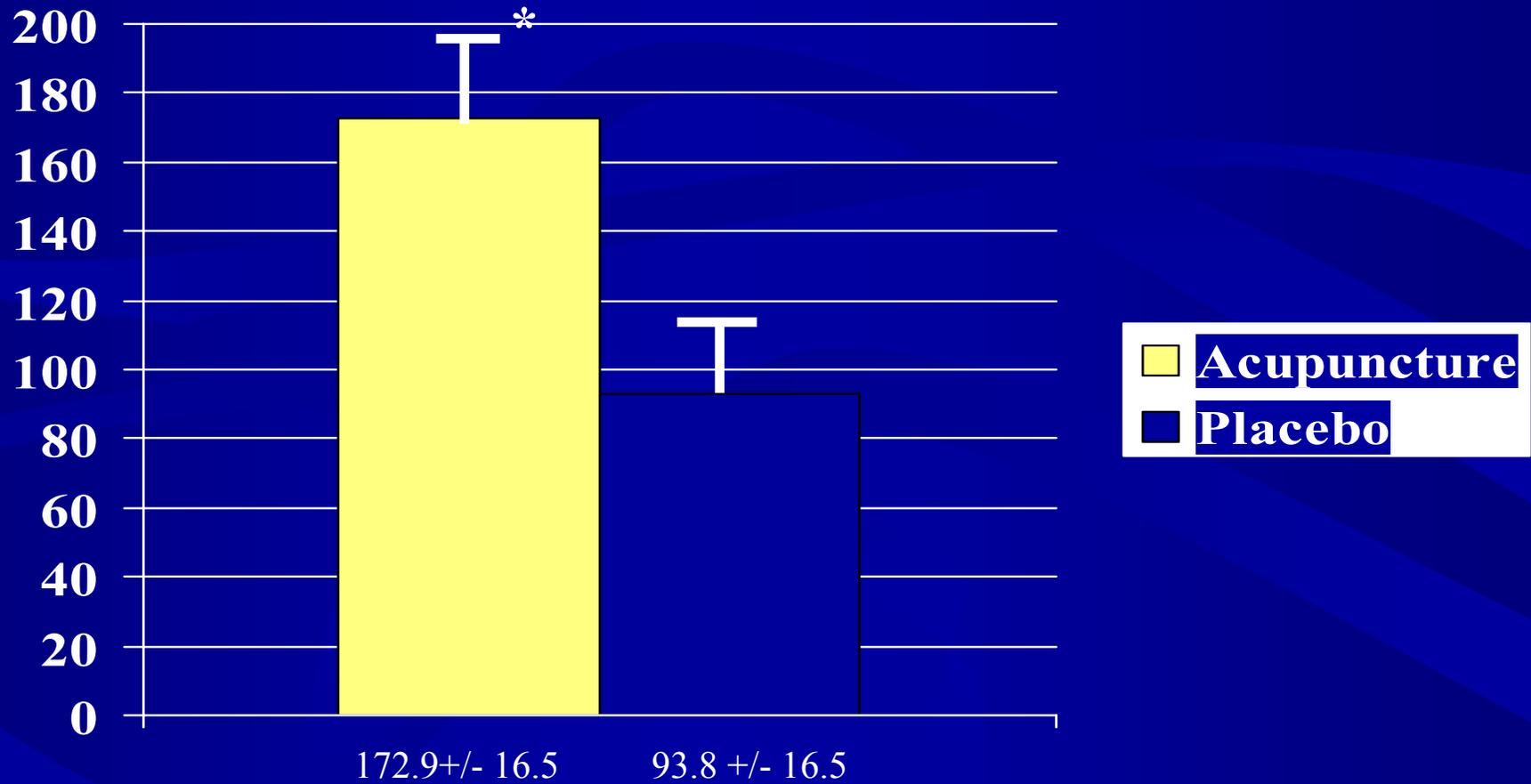
Follow Up

- 15 Minute Intervals
- 6 Hours On Site
- 24 Hours (1hr. interval)
- 7 Day Diary

Results

- N=39, 17 F, 22 M
- 32 Caucasian, 3 Hispanic, 3 Black, 1 Asian
- No Significant Difference:
 - Gender
 - Race
 - Age
 - Trauma rating
 - Local anesthetic
 - Psychological profile

Results



Mean Pain Free Duration Time

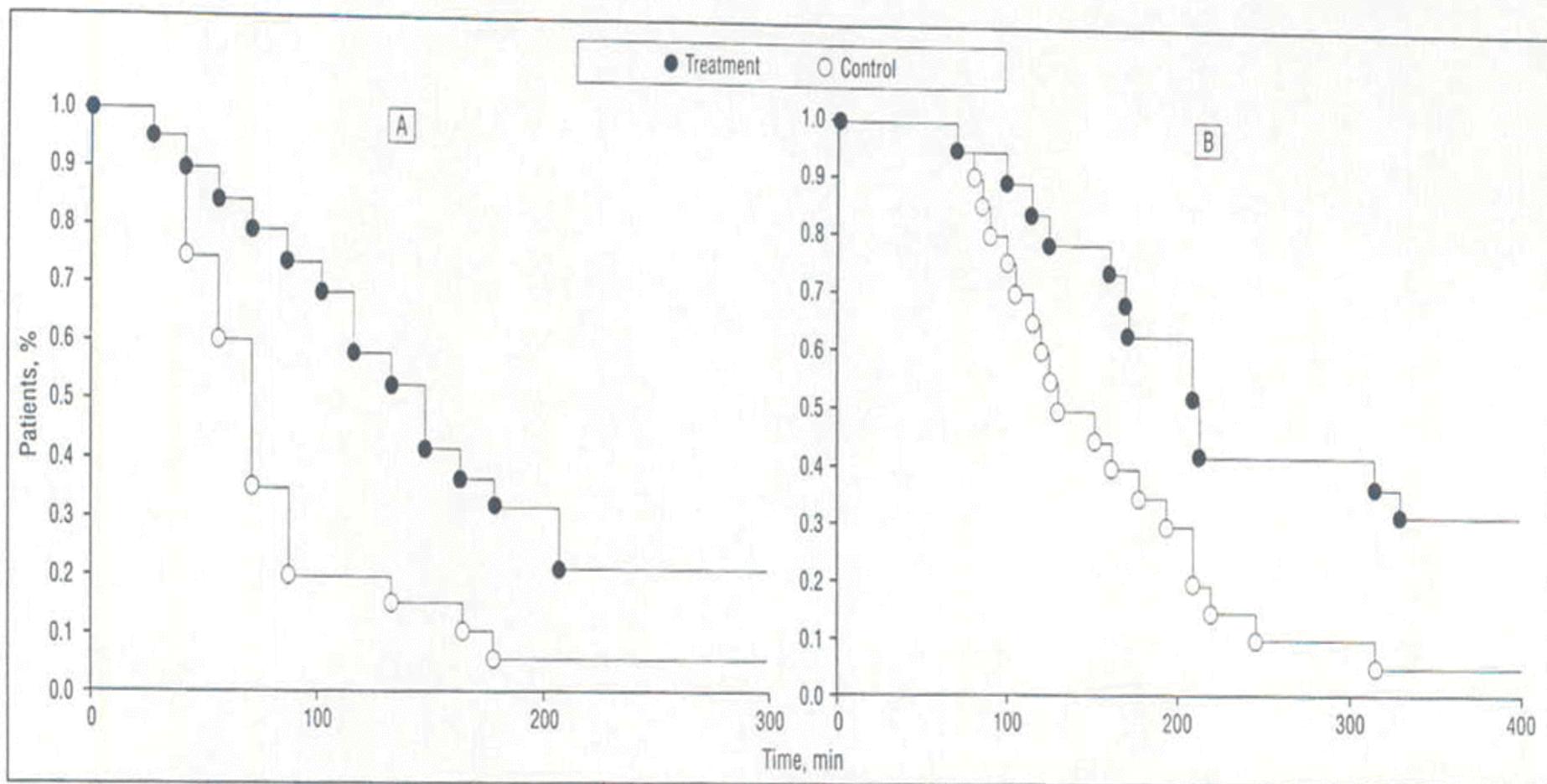


Figure 2. Comparisons between the acupuncture group ($n = 19$) and placebo group ($n = 20$) on Kaplan-Meier plots of survival using the log-rank test. A, Acupuncture group had longer pain-free time before reaching moderate pain than the placebo group ($P = .008$). B, Acupuncture group had longer pain survival time before taking rescue medication than the placebo group ($P = .01$).

Results

- Pain Medication (Tablets)- 24 hours
 - acupuncture - 1.1
 - placebo - 1.65
 - $p < 0.05$
- Pain Medication - 7 days
 - acupuncture - 7.7
 - placebo - 11.3
 - not significant

Pre-Treatment Evaluation

- Patient Motivation Assessment
- Patient Experience Assessment
- Patient Expectation Assessment

Post-Treatment Evaluation

- Patient Expectation Assessment
- Patient Stress Level Assessment
- Adverse Effect Assessment

Findings of Study

- Valid Placebo Model
- Acupuncture Effective
- No Adverse Effects

Clinical Trials of Acupuncture for Post-operative Dental Pain (Cont.)

Use of Acupuncture for Dental Pain: Testing a Model

PI: Lixing Lao, Ph.D., L.Ac.

- Two phase study
- Phase I: Three arm: (N = 120)
 - 1) Real acupuncture
 - 2) Sham insertion acupuncture control (adjacent)
 - 3) Sham insertion acupuncture control (distal)
- Phase II: Three arm: (N = 180)
 - 1) Real acupuncture
 - 2) Sham acupuncture control (determined by the phase I)
 - 3) Placebo acupuncture

Sham acupuncture - measuring nonspecific (placebo) effectiveness

Question: Is real acupuncture more effective than sham acupuncture?

Advantages:

- Resembles real acupuncture
- Patients can be blinded

Disadvantages: May produce nonspecific needling effects

Clinical Trial of Acupuncture for Non Pain Condition

A Controlled Study Using Acupuncture as an Adjuvant to Treat Chemotherapy - Induced Nausea and Vomiting

PI: Lixing Lao, Ph.D., L.Ac.

- To evaluate the effect of EA as an adjunctive therapy for chemo-induced N/V
- To measure the usefulness of EA in improving the quality of life of cancer patients
- To evaluate adverse effects of EA in the treatment procedure

Funded by U.S. Department of the Army Grant# : BC980536

Clinical Trial of Acupuncture for Non Pain Condition

A Controlled Study Using Acupuncture as an Adjuvant to Treat Chemotherapy - Induced Nausea and Vomiting (Cont.)

PI: Lixing Lao, Ph.D., L.Ac.

- Sample size: N=75
- Treatment Assignment
 - 1) EA 10 Hz (n=25)
 - 2) EA 100 Hz (n=25)
 - 3) Sham control (n=25)

Conclusion

- 1) Appropriate staging of trial design important
- 2) Make sure the acupuncture treatment is adequate and the control group is appropriate for the question being asked
- 3) Follow good clinical trials guidelines, including adequate randomization and allocation concealment, blinding procedures, adequate sample size and appropriate follow-up period
- 4) Collaborate between experienced CAM practitioners and experienced investigators.

Acknowledgements

The research projects were/are funded by

- **The National Center for Complementary and Alternative Medicine, NIH**
- **The Army Breast Cancer Research Program, Department of Defense.**

**Acupuncture Analgesia (AA):
What We Have Learned
From Animal Studies?**

Grant Zhang, Ph.D., L.Ac.

Complementary Medicine Program

University of Maryland School of Medicine

The Value of Animal Studies in AA

- **Reliable pain assessment**

- **Tail flick response (rat, mouse)**
- **Head jerk response (rabbit)**
- **Hot plate test (mouse)**
- **Vocalization (mouse)**
- **Paw withdrawal latency (rat)**

The Value of Animal Studies in AA

- **Choices of variety pain models**
- **Persistent inflammatory hyperalgesia (rat)**
- **Inflammatory arthritis (rat)**
- **Persistent neurological pain (rat)**
- **Cancer pain (rat)**

The Value of Animal Studies in AA

- **Availability of modern technology**
- **target-specific lesion**
- **nerve cell activity recording**
- **genetic techniques**
- **cellular marker tracing**
- **functional MRI**

The Value of Animal Studies in AA

- **Feasibility of control groups**
- **Sham control**
- **Point specific control**
- **Procedure control**
- **Vehicle control**
- **Naïve control**

Protocols of Animal Study

Animal receives acupuncture treatment



Test the changes of pain thresholds



Compare with control animals

Findings from Animal Studies

- **AA is caused by opioid release.**
- Opioid receptor antagonist, naloxone, blocks AA in mice (1976).
- Animals genetically deficient in opioid receptor show poor AA (1978).
- Opioid mRNA increased in neurons at spinal and supraspinal neurons (1983).
- Lesions of the arcuate nucleus abolishes AA (1990).
- Different electrical frequency of EA activates different opioid peptide (1992).

Findings from Animal Studies

- Acupuncture effect is conducted through type II and III afferent nerves.

Recording the impulses from the afferent nerves during acupuncture treatment shows type II and III afferent nerves were specifically activated.

The Mechanism of Acupuncture-induced Analgesia

- **Release neurotransmitters (e.g., opioids)**
- **Gate control**
- **Modulating activities of functional structures in the CNS.**

Limitations

- **No pathological conditions**
- **Transient condition (minutes)**
- **Restrained animals**
(stress-induced analgesia?)

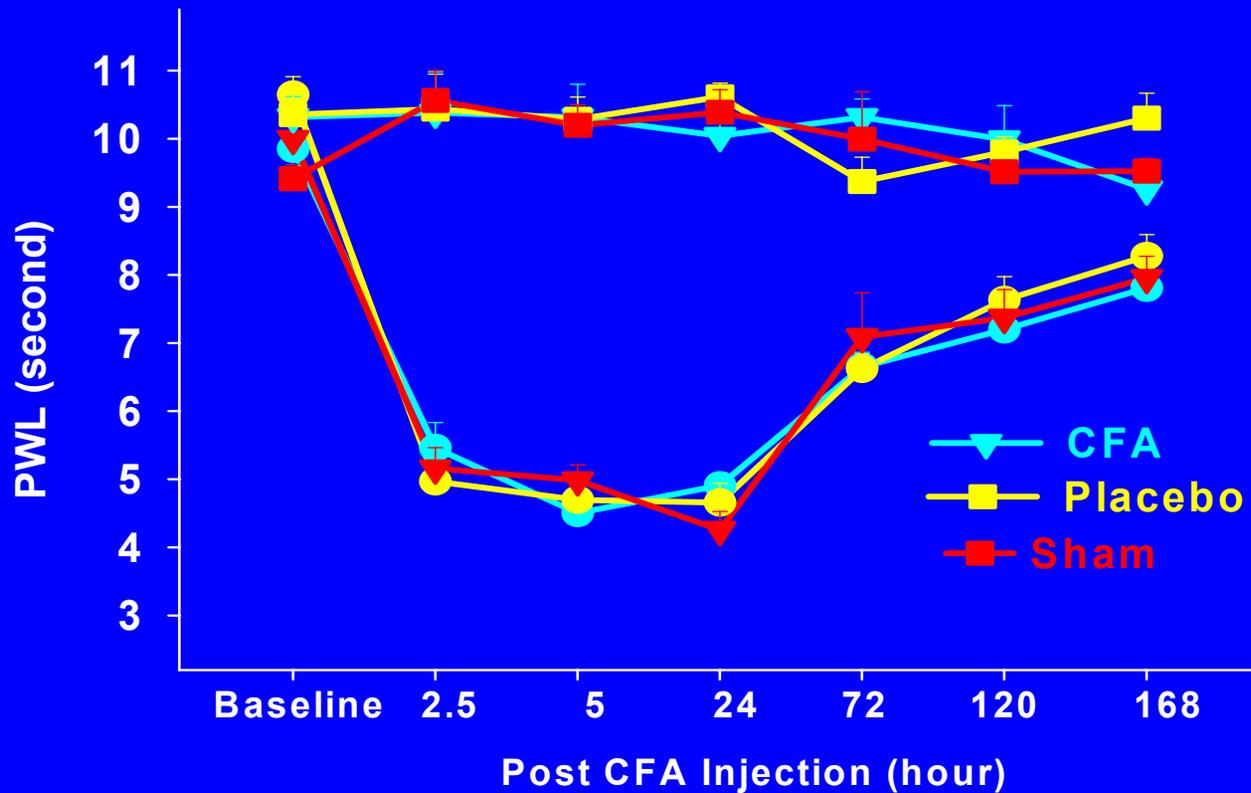
Localized Inflammatory Hyperalgesia Model

- Induction of inflammation: One hind paw of the rat was injected with complete Freund's adjuvant (CFA).
- Measure of hyperalgesia: A noxious heat stimulus was applied onto the plantar surface of the hind paw and PWL was recorded.

Characteristics

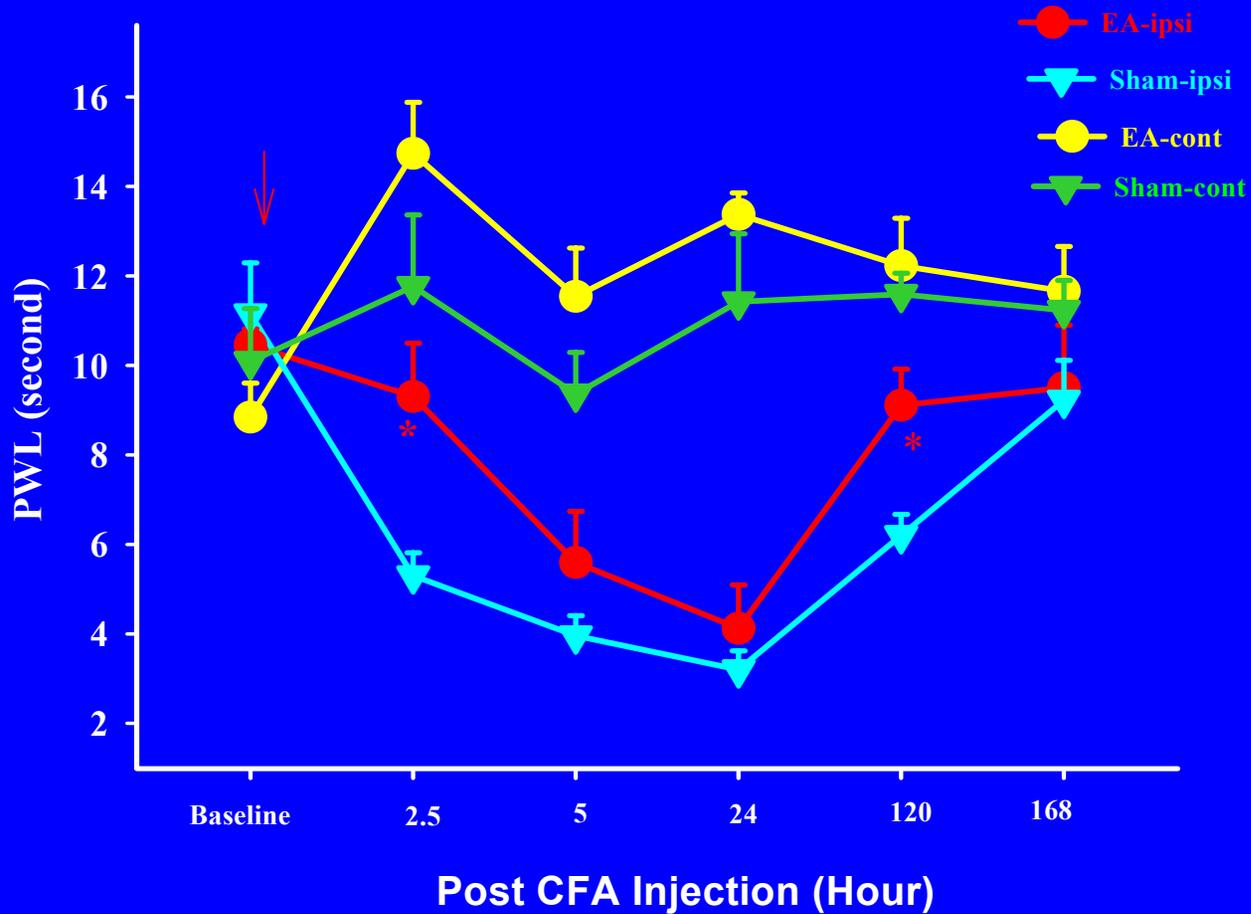
- **Clinic relevance (pathological condition)**
- **Acute and sub-acute condition (up to 10 days).**
- **Non-restrained animals.**
- **The hyperalgesia can be assessed quantitatively.**

Paw Withdrawal Latency (PWL) of Control Rats



The Effect of EA On Thermal Hyperalgesia

10 Hz, 3V, 0.01ms, 20 minutes

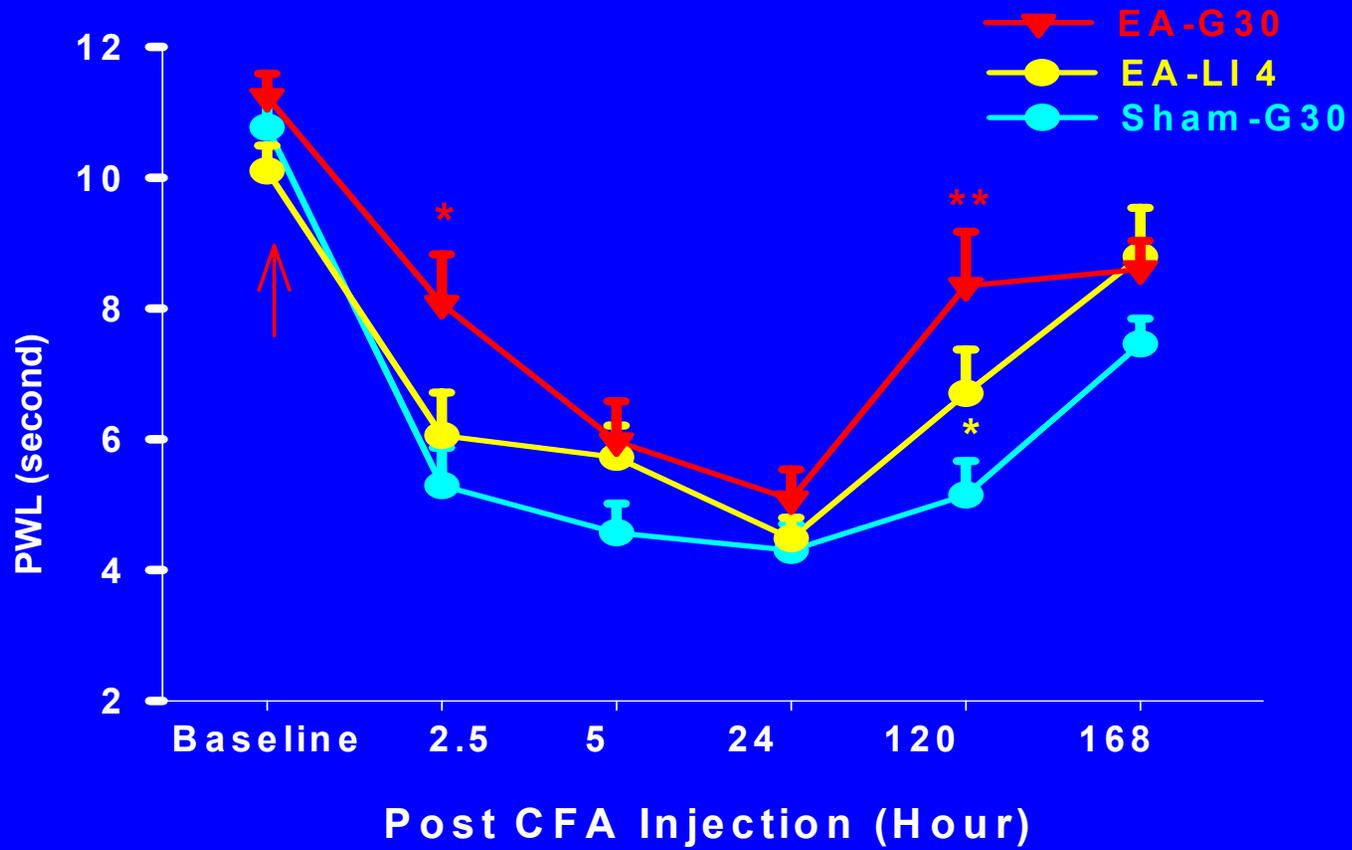


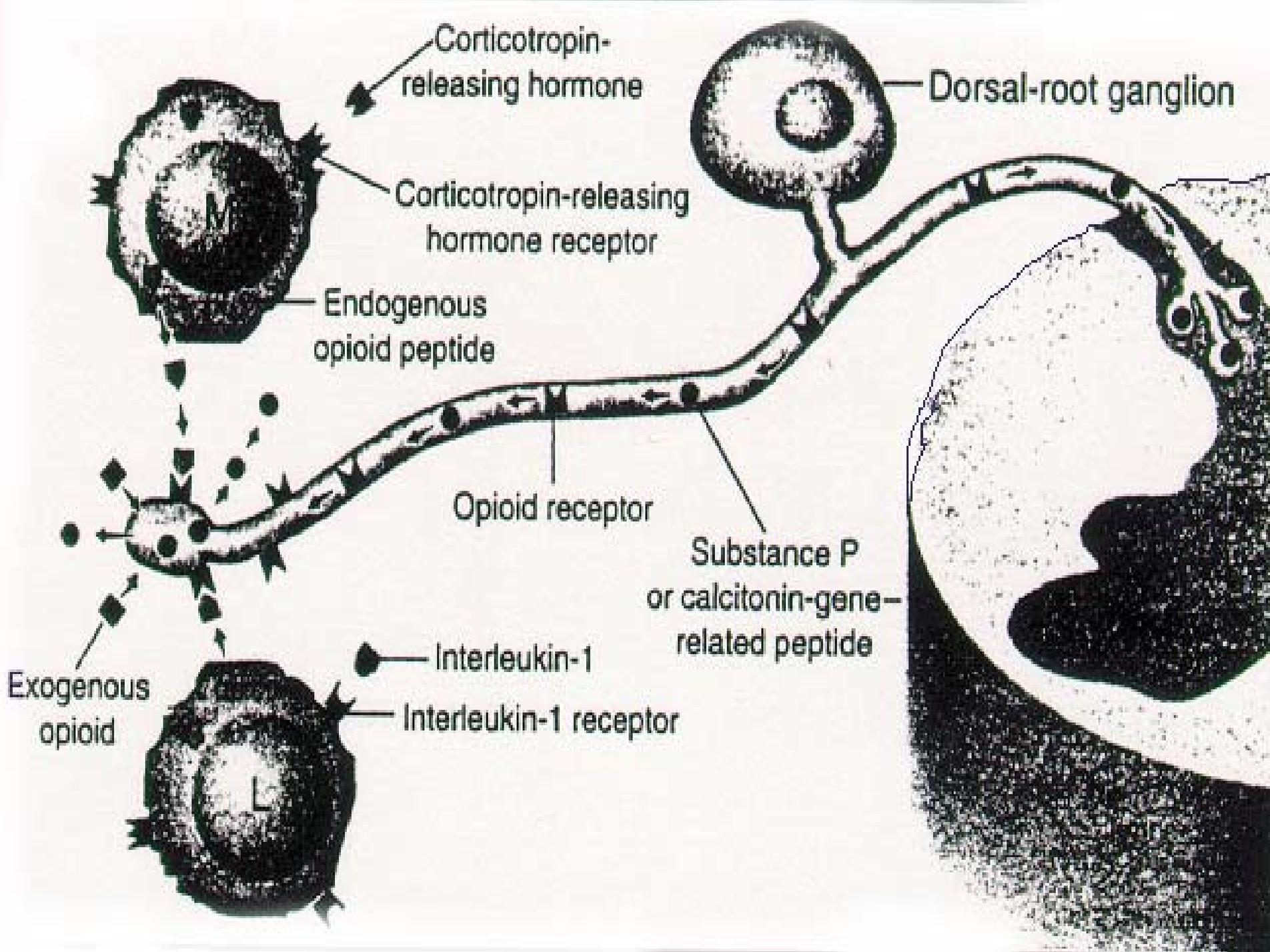
Summary of Behavioral Study: P value as compared to sham

Frequency (Hz)	Current (mA)	2.5 h	5 h	24 h	72 h	120 h	168 h
10	1						
	2	0.032					
	3	0.019		0.047		0.032	0.044
50	1						
	2	0.049					
	3	0.033					
100	1						
	2	0.034					
	3	0.0029	0.0043	0.0038			

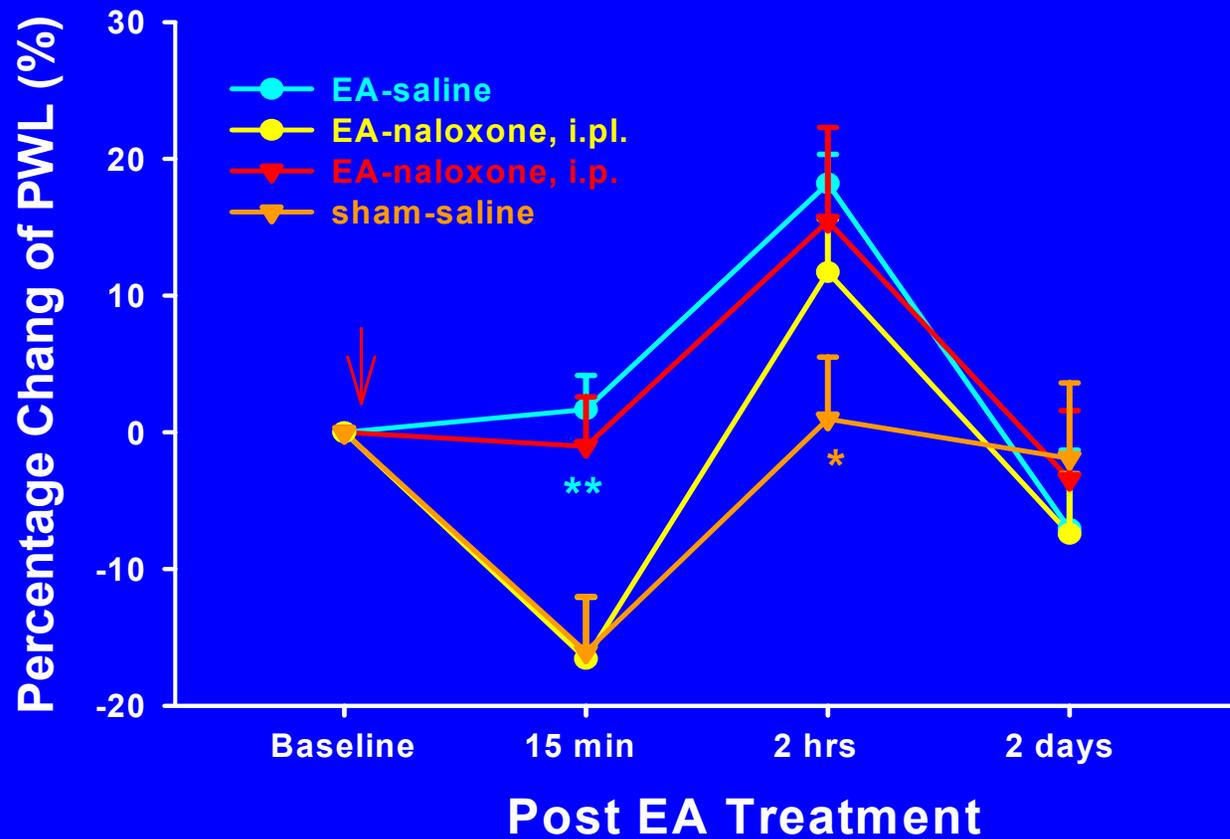
The Effect of EA on Hyperalgesia: G30 vs. LI4

10 Hz, 3 mA, 0.01ms, 20 min

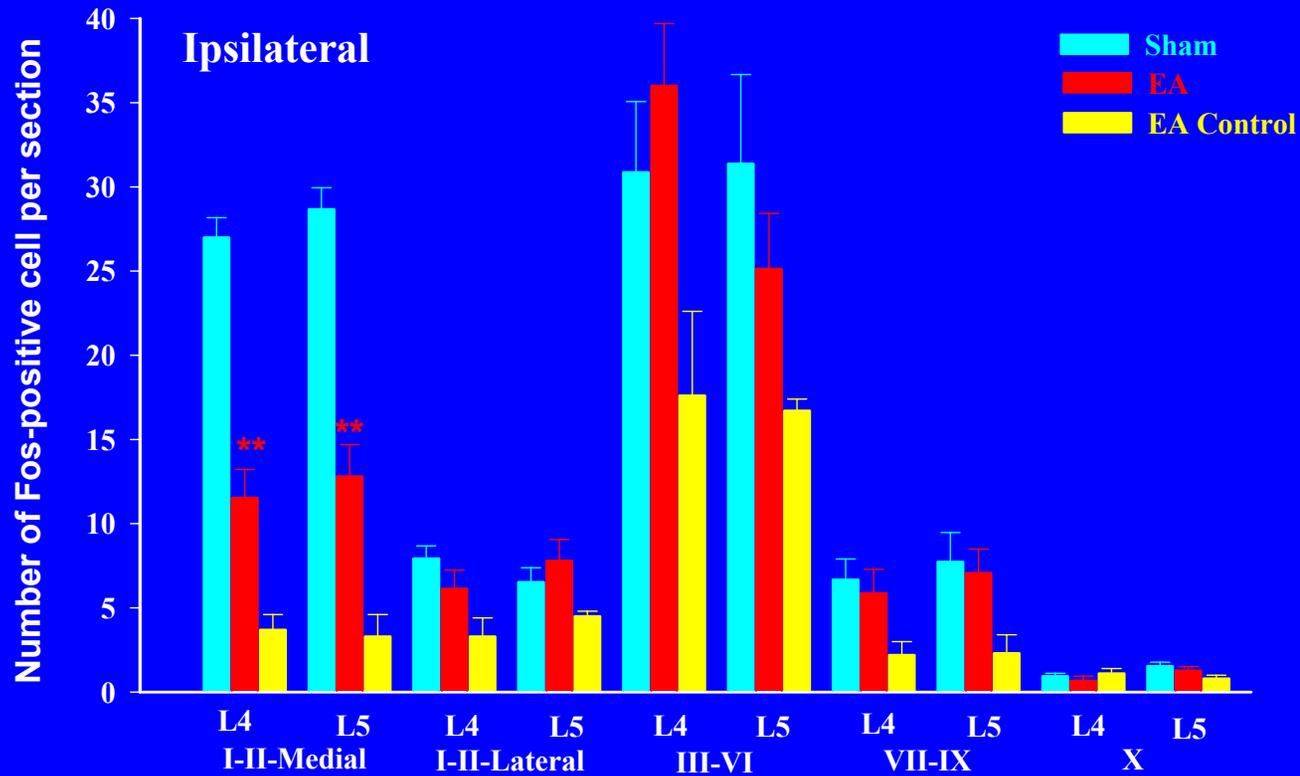




The Effect of Local naloxone on EA Analgesia



Fos LI Neurons At L4/L5 Spinal Cord



Inflammatory Arthritis Model

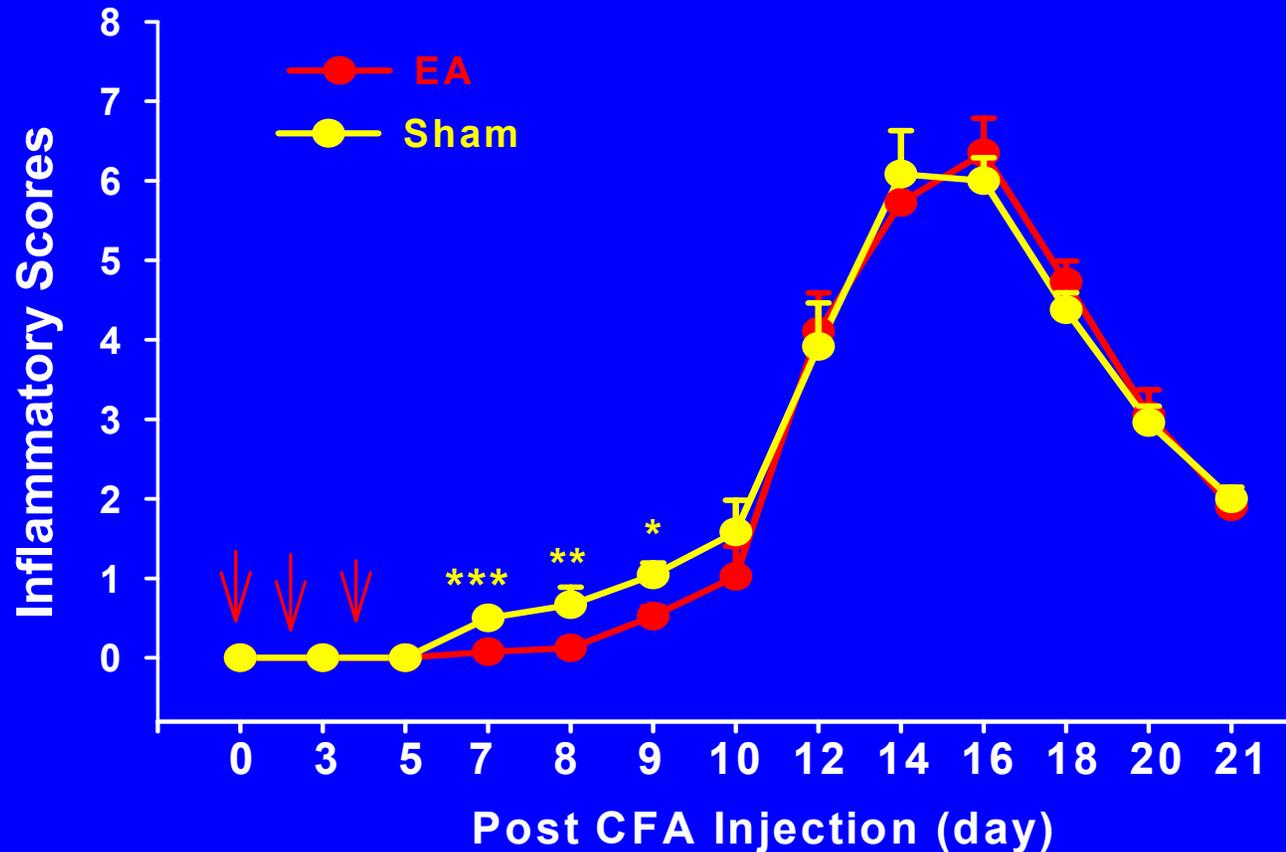
- Induction of inflammation: complete Freund's adjuvant (CFA) was injected into the subcutaneous tissue of the rat.
- Measure of disease: Scores are given according to the number of paws developing edema and the severity of the edema.

Characteristics

- **Pathologically similar to RA in human.**
- **There is an incubation period (5 to 7 d).**
- **It runs a chronic course (4 to 6 weeks).**
- **Immunological assays are available.**

The Effect of EA on Inflammation

30 Hz, 2mA, 0.01ms, 30 minutes



Summary and Conclusions

- **The studies on the mechanism of AA have benefited tremendously from the animal studies.**
- **Proper selection of animal model is important.**
- **More animal studies are needed to elucidate the mechanism of acupuncture.**

ACKNOWLEDGEMENTS

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Chengsi Yu, Ph.D.; Xiaoya Wang

- **Collaborations**

Ke Ren, Ph.D.; Kamal Modgil, Ph.D., M.D.;
Christoph Stein, M.D.

- The studies are supported by grants from NCCAM, NIH
(AT00084: P.I. L. Lao; AT00279: P.I. G. Zhang)

Future Directions in Acupuncture Research: Relevance to Cancer Treatment

Richard Hammerschlag, PhD
Research Director
Oregon College of Oriental Medicine
Portland, OR

Future Directions in Acupuncture Research

- Clinical research: efficacy
- Physiological research: mechanism

Alternative Medicine Meets Science

Fontanarosa PB, Lundberg GD (1998)

JAMA 280:1618-1619.

“There is no alternative medicine. There is only *scientifically proven*, evidence-based medicine supported by solid data or *unproven medicine*, for which scientific evidence is lacking. Whether a therapeutic practice is ‘Eastern’ or ‘Western’, is unconventional or mainstream, or involves mind-body techniques or molecular genetics, is largely irrelevant except for historical purposes and cultural interest.”



The next decade of clinical research in acupuncture will see:

- Improved quality of clinical trial design
- Increased reflection of clinical practice in clinical research
- Improved reporting of clinical trials (STRICTA)
- Increased testing of acupuncture and herbs as adjunctive care for (i) cancer-related symptoms and (ii) biomedical treatment side-effects
- Increased testing of traditional Chinese medicine as an adjunctive *system* of care

Improved quality of clinical trial design

- 1997: NIH Consensus Development Conference on Acupuncture agreed – research design in acupuncture trials has been relatively poor
- 1998: OAM RFA to improve methodology in clinical trials of acupuncture (7 proposals funded)
- Impact of systematic reviews of acupuncture
- Research training of CAM px's at NCCAM Centers
 - Precedent for accepting LAc's as fellows (OCCAM)

Increased reflection of clinical practice in clinical research

- Protocols will allow more individualized treatment:
 - Within explanatory trials
 - Irritable Bowel Syndrome: compare acupuncture trial (Fireman et al, 2001) to Chinese herb trial (Bensoussan et al, 1998)
 - Migraine (Gao et al, 1999)
 - MS-specific fatigue (Hammerschlag et al, 2001)
 - Within pragmatic trials
 - NHS (UK) trials of Low-back pain (Thomas et al, 1999) and Migraine (Vickers et al, 1999)
 - Depression (Allen et al, 1998)

Improved reporting of clinical trials

STandards for Reporting Interventions in Controlled Trials of Acupuncture (STRICTA)

(MacPherson et al, 2002)

- Modification of CONSORT
- Consensus process
- Publication of STRICTA:

Acupunct Med; Clin Acupunct Orient Med;

Complement Ther Med; J Altern Complement Med;

Med Acupunct

Increased testing of acupuncture and herbs as adjunctive care for cancer-related symptoms and biomedical tx side effects

(Wong et al, Cancer Treatment Rev 27:235-246, 2001)

- Treat the “terrain”: Immune system, microcirculation, bioelectromagnetic field
- Lessen the symptoms: Pain, depression, breathlessness
- Potentiate biomedical treatment: sensitize tumor to radiation
- Suppress side-effects of biomedical treatment: nausea, fatigue, neutropenia, xerostomia

Electroacupuncture for control of myeloablative chemotherapy-induced emesis: a randomized controlled trial

Shen et al (2000) JAMA 284:2755-2761

- 104 women undergoing bone-marrow transplant for breast cancer, randomized to:
 - 1) 2-10 Hz el-acu at P6 & ST36, 20 min/day, 5 days
 - 2) shallow needling with mock electrostim, same tx schedule, at 2 non-acupoint sites
 - 3) no adjunctive needling
- All groups received identical 4-day high dose chemo and standard antiemetic meds

Shen et al (2000) JAMA 284:2755-2761

- Median number of emesis episodes over 5 days:

<u>Group</u>	<u># episodes</u>	<u>p</u>
1 (acu)	5	<0.001 (1 vs 2)
2 (sham)	10	0.01 (2 vs. 3)
3 (no tx)	15	

- Patients in groups 1 & 2 unable to guess whether they received true or sham acu

*Testing traditional Chinese medicine
as an adjunctive system of care*

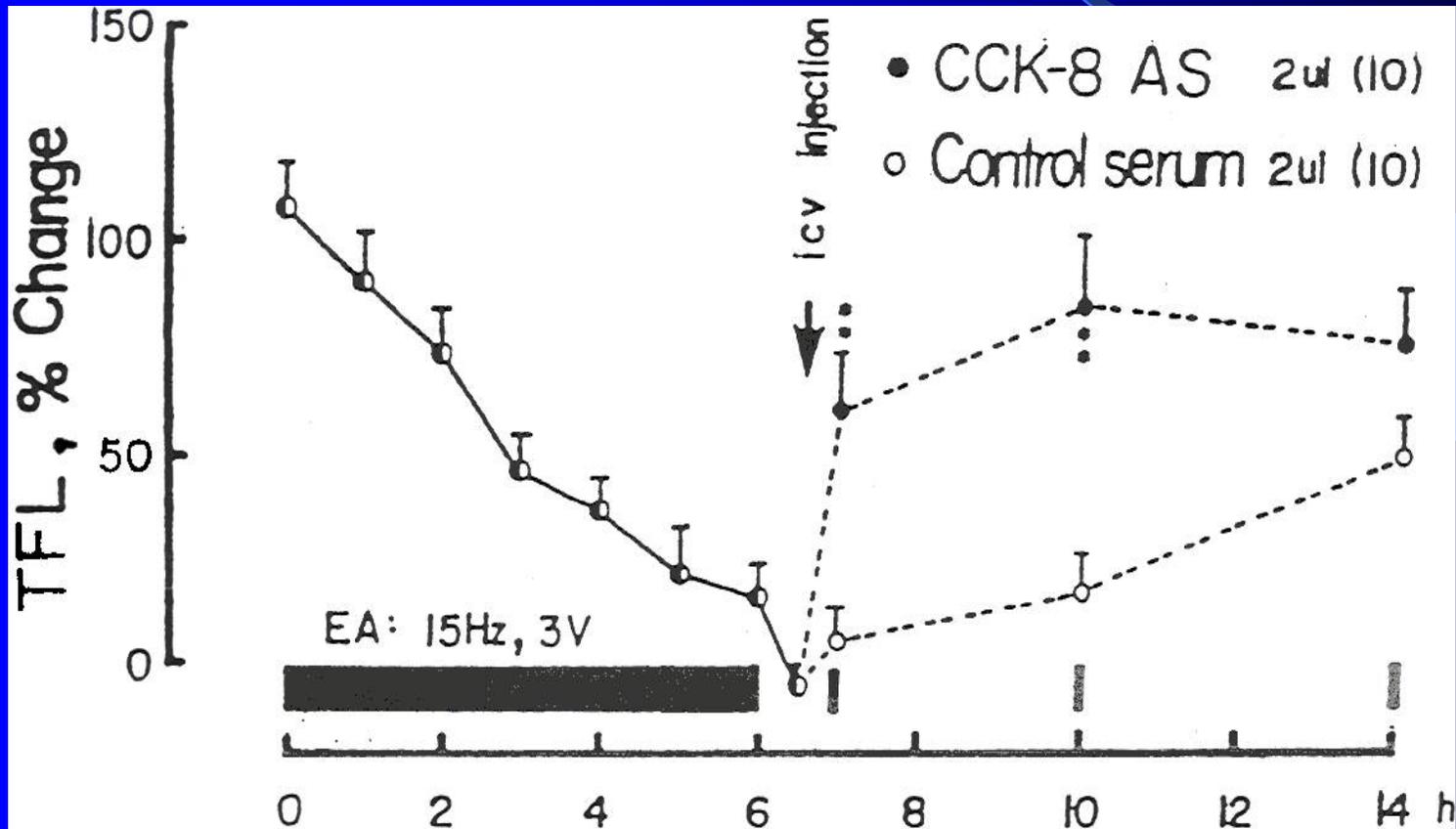
Developing a model of integrative care

Physiological research in acupuncture
is usually guided by the question:

*“What biomedical changes correlate with
acupuncture effectiveness?”*

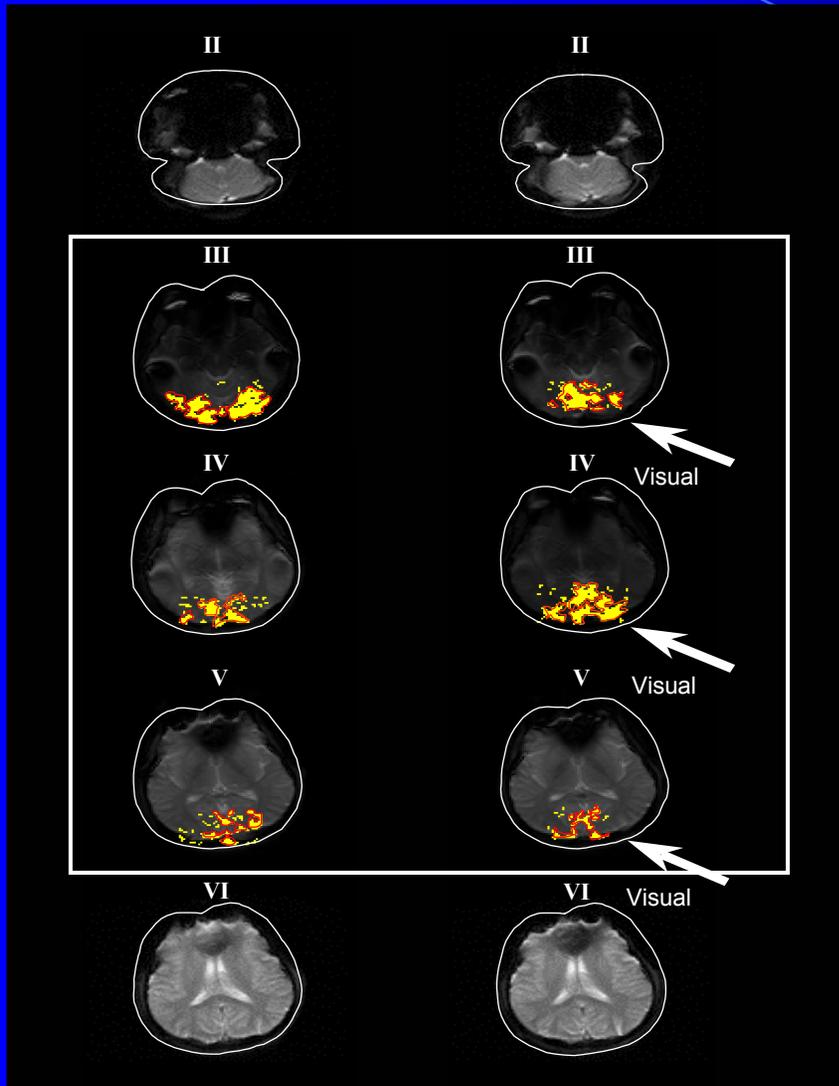
Reversal of Electroacupuncture Tolerance by CCK-8 Antiserum

Han (1985) *Neuropeptides* 5:399-402



Acupuncture-related fMRI signals

Cho et al (2001) In: *Clinical Acupuncture: Scientific Basis*



(a) Visual
(Reference)

(b) Acupoint
(GB37)

Evidence of:

- a) meridians?
- b) neural pathways?
- c) unknown signaling system?

Physiological research can be guided by a different question:

- *What can acupuncture tell us about how the body functions that the bio-medical model does not encompass?*

Acupuncture's Challenges to the Biomedical Model

- Acupuncture promotes healing in a homeostatic manner
- Clinical effectiveness can occur without mechanical transduction

Evidence for homeostatic healing

- Cardiovascular

- Blood pressure and heart rate normalized in hypotensive and hypertensive rats (Yao,1993)
- Blood flow & heart rate normalized in humans (Ballegaard et al,1993)

- Immunology

- Salivary IgA levels normalized in humans (Yang et al,1989)

Consider the range of techniques for stimulating acupoints:

- 1) “Deep” needling with electrostim
- 2) “Deep” manual needling
- 3) “Shallow” manual needling
- 4) Non-invasive *Toyo Hari* “needling”
- 5) Qigong

The New Cell Biology

- The cell is not a bag of organelles
- Most biochemical reactions occur in a (semi) *solid state*
- Many macromolecules function as *liquid crystals* and *semiconductors*

Structure/Function Views from the New Cell Biology

- Continuum between extracellular matrix and cytoskeleton
- Rapid response of liquid crystals to changes in pressure, temperature, electric and magnetic fields
- Bound water at surface of collagen helix allows “rapid jump conduction” of protons (proticity)

Organism as an Informational Continuum

- Tensegrity system (Ingber, 1998)
- Liquid crystalline matrix (Ho, Knight, 1998)
- Electromagnetic field receptors (?)
(Blank et al, 2001)
- Basis of energy medicine (?) (Oschman, 2000)